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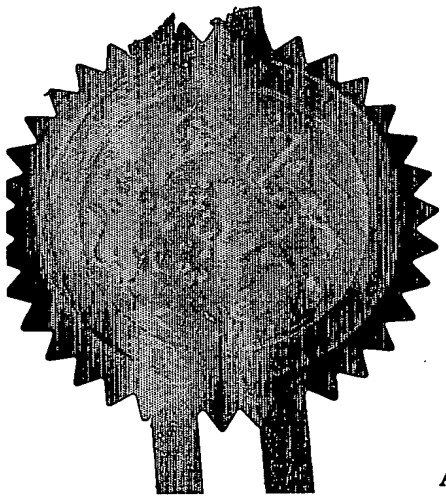

Signed Andrei Gerasj

Dated 22 April 2003

Patents Form 1/77

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The Patent Office

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The Patent Office
Cardiff Road
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1. Your reference — MG/HG/P33023

2. Patent application number
(The Patent Office will fill in his part) — 0207282.5

28MAR02 E707164-1 C69803
P01/7700 0.00-0207282.5

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)* 473587 003

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)*

Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GlaxoSmithKline
Corporate Intellectual Property CN925.1
980 Great West Road
BRENTFORD
Middlesex TW8 9GS.

Patents ADP number *(if you know it)* 807 255506

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

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Continuation sheets of this form	
Description	13
Claim(s)	2
Abstract	
Drawings	

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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application.
Signature _____ Date 27-Mar-02
S C Hockley

12. Name and daytime telephone number of person to contact in the United Kingdom: S C Hockley 01279 644355

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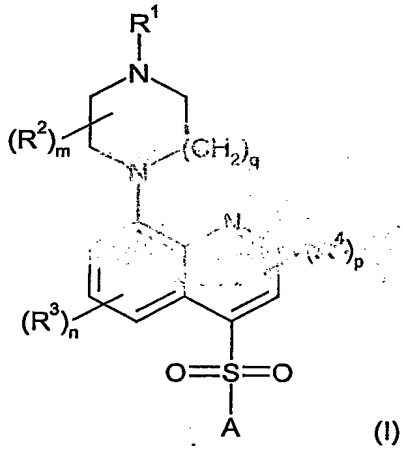
NOVEL COMPOUNDS

This invention relates to novel quinolinyl sulphonyl compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

WO 98/27081, WO 99/02502, WO 99/37623, WO 99/42465 and WO 01/32646 (SmithKline Beecham plc) disclose a series of aryl sulphonamide and sulphoxide compounds that are said to be 5-HT_6 receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders. WO 97/03069 (Glaxo Group Limited) and WO 96/09294 (The Wellcome Foundation Limited) both describe a series of substituted quinolines and quinazolines as protein tyrosine kinase inhibitors. JP 02262627 (Japan Synthetic Rubber Co) describes a series of substituted quinoline derivatives useful as wavelength converting elements.

A structurally novel class of compounds has now been found which possess affinity for the 5-HT_6 receptor. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 independently represent hydrogen or C_{1-6} alkyl or R^1 is linked to R^2 to form a group $(CH_2)_2$, $(CH_2)_3$ or $(CH_2)_4$;

m represents an integer from 1 to 4, where m is greater than 1, two R^2 groups may instead be linked to form a group $(CH_2)_2$, $(CH_2)_3$ or $(CH_2)_4$;

R^3 and R^4 independently represent hydrogen, halogen, cyano, $-CF_3$, $-CF_3O$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR^5R^6$;

R^5 and R^6 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

n represents an integer from 1 to 3;

p and q independently represent 1 or 2.

A represents a group $-Ar^1$ or a group $-Ar^2$-Ar^3;

Ar^1, Ar^2 and Ar^3 independently represent an aryl group or a heteroaryl group, both of which may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $CONR^7R^8$ or $SO_2NR^7R^8$, wherein R^7 and R^8 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom; or solvates thereof.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes phenyl and naphthyl.

The term "heteroaryl" is intended to mean a 5 or 6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like. Heteroaryl groups, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom except where otherwise indicated above.

It will be appreciated that wherein the above mentioned aryl or heteroaryl groups have more than one substituent, said substituents may be linked to form a ring, for example a carboxyl and amine group may be linked to form an amide group.

Preferably, R^1 represents hydrogen.
Preferably, m represents 1.
Preferably, R^2 represents hydrogen.
Preferably, n represents 1.
Preferably, R^3 represents hydrogen or a halogen atom.
Preferably, p represents 1.

Preferably, R^4 represents hydrogen or methyl (particularly 2-methyl).

Preferably, q represents 1.

When A represents $-Ar^2Ar^3$, Ar^3 is preferably linked to Ar^2 via a carbon atom of Ar^3.

Preferably, A represents $-Ar^1$.

Preferably, $-Ar^1$ is phenyl or pyridyl optionally substituted by one or more halogen atoms or cyano, trifluoromethoxy or trifluoromethyl groups, more preferably unsubstituted phenyl, 2-fluorophenyl, 3-fluorophenyl or 3-chlorophenyl.

Preferred compounds according to the invention include examples E1-E7 as shown below, or a pharmaceutically acceptable salt thereof.

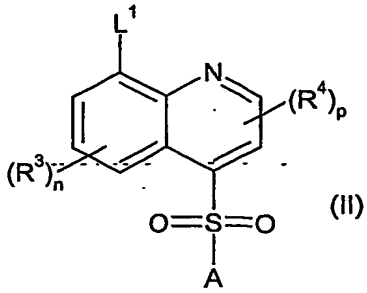
The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

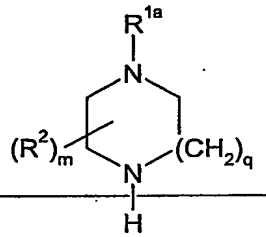
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)



(II)

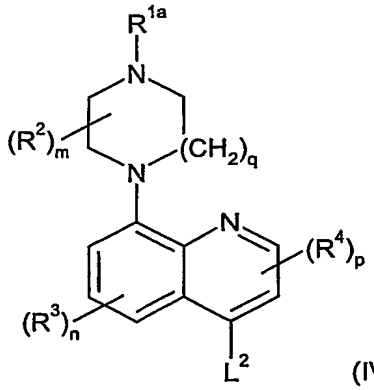
wherein R^3, R^4, n, p and A are as defined above and L^1 represents a leaving group, such as a halogen atom,
with a compound of formula (III)



(III)

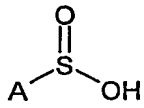
wherein R^{1a} is as defined for R^1 or an *N*-protecting group such as *tert*-butyloxycarbonyl (t-Boc), R^2, m and q are as defined above, followed by subsequent deprotection as necessary;

(b) reacting a compound of formula (IV)



(IV)

wherein R^{1a} is as defined for R^1 or an *N*-protecting group such as trifluoroacetyl, R^2, R^3, R^4, m, n, p and q are as defined above and L^2 represents a leaving group such as a halogen atom,
with a compound of formula (V)



(V)

(or a compound of formula A-SH followed by a subsequent oxidation step), wherein A is as defined above, followed by subsequent deprotection as necessary;

(c) deprotecting a compound of formula (I) which is protected; and thereafter optionally

(d) interconversion to other compounds of formula (I) and/or forming a pharmaceutically acceptable salt and/or solvate.

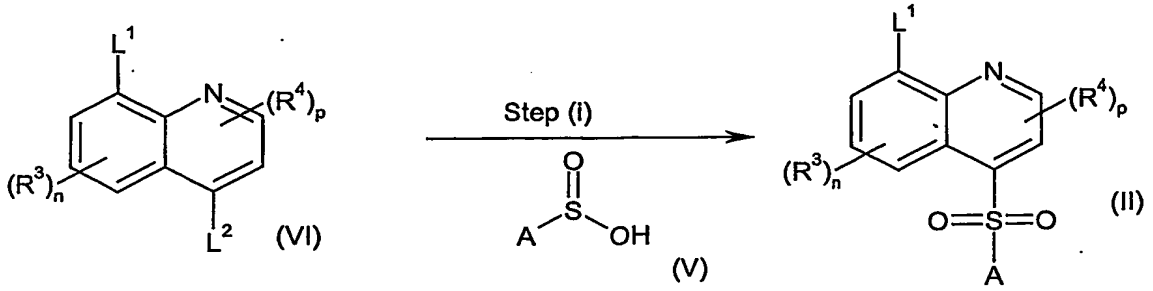
Process (a) typically comprises the use of a palladium catalyst, eg. palladium acetate in the presence of a suitable ligand, eg. BINAP and a suitable base, eg. caesium carbonate in a suitable solvent, eg. dioxane.

Process (b) involving the use of a compound of formula (V) is typically carried out under basic conditions, for example using the sodium salt of the sulfinic acid compound of formula (V) in the presence of a suitable solvent, eg. dimethylformamide. Process (b) involving the use of a compound of formula A-SH typically comprises the use of basic conditions e.g. by using a suitable salt of the compound A-SH (e.g. the sodium salt) in the presence of a suitable solvent, eg. dimethylformamide, followed by use of a suitable oxidant such as 3-chloroperbenzoic acid, peracetic acid or potassium monopersulfate.

In processes (a), (b) and (c), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butyloxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric or trifluoroacetic acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-COCF3) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (d) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation.

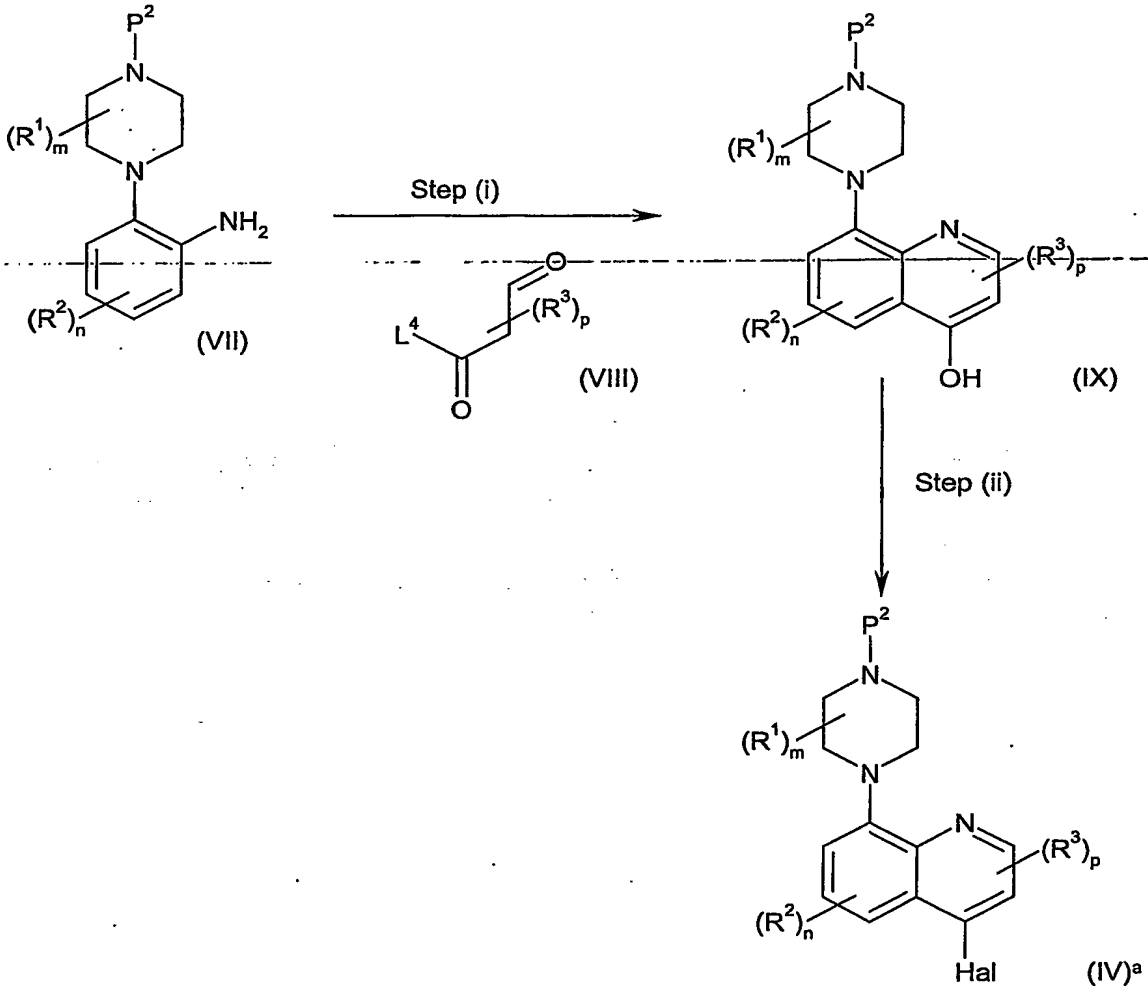
Compounds of formula (II) may be prepared in accordance with the following process:



wherein R^3, R^4, n, p, A, L^1 and L^2 are as defined above.

Step (i) is typically carried out under basic conditions, for example using the sodium salt of the sulfinic acid compound of formula (V) in the presence of a suitable solvent, eg. dimethylformamide. Alternatively this transformation may be carried out using a compound of formula A-SH and subsequent oxidation in a manner similar to that described for process (b).

Compounds of formula (IV) wherein L^2 represents a halogen atom (Hal) may be prepared in accordance with the following process:



wherein R^1, R^2, R^3, m, n and p are as defined above, L^4 represents a suitable leaving group, eg. an alkoxy group and P^2 represents a suitable protecting group, eg. trifluoroacetyl.

Step (i) typically comprises an initial condensation reaction under acidic conditions, followed by a thermal cyclisation of the resulting enamine in the presence of a suitably high boiling solvent, eg. diphenyl ether.

Step (ii) typically comprises the use of a suitable phosphorus halide or phosphoryl halide at an elevated temperature.

Compounds of formulae (III), (V), (VI), (VII) and (VIII) are commercially available, may be prepared using procedures described herein or by analogous methods thereto or according to known methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the 5-HT_6 receptor and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. Alzheimers disease, age related cognitive decline and mild cognitive impairment), Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome). Compounds of the invention are also expected to be of use in the treatment of obesity.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, obesity, anxiety and cognitive memory disorders

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal

administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

~~For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the~~ invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 200 mg, for example 20 to 40 mg; and such unit doses will preferably be administered once a day, although administration more than once a day may be required; and such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

8-Iodo-4-phenylsulfonylquinoline (D1)

Phenylsulfinic acid sodium salt (621 mg, 2.7 mmol), dissolved in DMF (10 ml), was added to a stirred solution of 4-bromo-8-iodoquinoline (300 mg, 0.89 mmol) in DMF (10 ml) at room temperature under argon. Reaction then stirred at 100 °C for 16 h. Reaction mixture was then diluted with water (50 ml) and extracted with EtOAc (3 x 50 ml). Combined organic layers were washed with brine (50 ml), dried ($MgSO_4$) and the solvents evaporated *in vacuo*. Purification by flash chromatography (EtOAc / hexane) gave the title product as a yellow solid (306 mg).

^{1}H NMR ($CDCl_3$) : δ 7.32-7.39 (1H, t), 7.49-7.65 (3H, m), 7.96-8.00 (2H, m), 8.21-8.23 (1H, d), 8.40-8.44 (1H, dd), 8.67-8.71(1H, dd), 9.19-9.21(1H, d).

MS : $C_{15}H_{10}INSO_2$ requires 395; found 396 (MH^+)

Description 2

8-(4-*tert*-Butyloxycarbonyl-piperazin-1-yl)-4-phenylsulphonyl-quinoline (D2)

2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (48 mg, 0.08 mmol), $Pd(OAc)_2$ (11.4 mg, 0.05 mmol) and Cs_2CO_3 (248 mg, 0.75 mmol) were combined in dioxane (5 ml) under argon and sonicated for 45 min. 1-Boc piperazine (236 mg, 1.28 mmol) and 8-iodo-4-phenylsulfonylquinoline (D1) (200 mg, 0.51 mmol) were combined in dioxane (5 mL) and added to the resulting blood red solution. Reaction was then left to heat at 100 °C for 16 h. The solvent was then evaporated *in vacuo* and the residue partitioned between DCM (10 ml) and water (10 ml). The organic layer was removed and the aqueous layer re-extracted with DCM (10 ml). Combined organics were washed with sat. NaHCO$_3$ (20 mL), 10% citric acid solution (20 mL), brine (20 mL), dried ($MgSO_4$) and the solvents evaporated *in vacuo*. Purification by Flash chromatography (EtOAc/hexane) gave the title product as a yellow oil (51.2 mg).

^{1}H NMR ($CDCl_3$) : δ 1.49 (9H, s), 3.27-3.31 (4H, m), 3-71-3.75 (4H, m), 7.14-7.15 (1H, dd), 7.48-7.59 (4H, m), 7.96-7.99 (2H, m), 8.17-8.19 (1H, d), 8.22-8.25 (1H, dd), 9.07-9.09 (1H, d).

MS : $C_{24}H_{27}N_3SO_4$ requires 453; found 454 (MH^+)

Description 3

2-(4-Methylpiperazin-1-yl) nitrobenzene (D3)

1-Fluoro-nitrobenzene (17.7 ml, 0.168 mol), 1-methyl-piperazine (16 g, 0.16 mol) and K_2CO_3 (24.3 g, 0.176 mol) were combined in DMSO (140 ml) and heated to 140 °C for 16 h. The reaction mixture was then cooled and partitioned between water (300 ml) and EtOAc (300ml). The aqueous was re-extracted with EtOAc (300 ml) and the combined organics washed with water (600 ml), dried ($MgSO_4$) and the solvents evaporated *in vacuo* to give the title product as a dark orange oil (35.35 g)

^{1}H NMR ($CDCl_3$) : δ 2.36 (3H,s), 2.56-2.62 (4H, m), 3.08-3.10 (4H, m), 7.02-7.05 (1H, t), 7.14-7.16 (1H, dd), 7.45-7.50 (1H, m), 7.74-7.77 (1H, dd)

Description 4

2-(4-Trifluoroacetyl-piperazin-1-yl) nitrobenzene (D4)

α-chloroethylchloroformate (7.7 ml) was added to a solution of 2-(4-Methyl piperazin-1-yl) nitrobenzene (D3) (10 g, 45.2 mmol) in DCM (150 ml) with rapid stirring. Diisopropylethylamine (DIPEA) (12.4 ml) was then added and the solution refluxed for 1 h. The solvent was then evaporated *in vacuo* and the residue refluxed in MeOH (150 ml) for 1h. The solvent was then evaporated *in vacuo*, and the residue taken up in DCM (150ml), under argon. Solution then cooled in an ice-bath and 2,6-lutidine (12.2 ml) added. Trifluoroacetic anhydride (6 ml) in DCM (50 ml) was then added dropwise and the solution left to stir for 16 h. The solution was washed with 10% citric acid solution (2 x 200 ml), brine (200 ml), dried ($MgSO_4$) and solvents evaporated *in vacuo*. Purification by flash chromatography (EtOAc/hexane) gave the title product as an orange solid (3.48 g).

^{1}H NMR ($CDCl_3$) : δ 3.11-3.15 (4H, m), 3.77-3.79 (2H, m), 3.85-3.88 (2H, m), 7.17-7.21 (2H, m), 7.53-7.57 (1H, m), 7.82-7.84 (1H, dd)

MS : $C_{12}H_{12}F_3N_3O_2$ requires 303; found 304 (MH^+)

Description 5

2-(4-Trifluoroacetyl-piperazin-1-yl)aniline (D5)

2-(4-trifluoroacetyl-piperazin-1-yl) nitrobenzene (D4) (3.34 g, 11 mmol) was dissolved in EtOH (150 ml) under argon and palladium (10 % Pd on C paste, 300 mg) was added. Reaction mixture was hydrogenated at 1 atm for 16 h. The solution was then filtered through celite and concentrated to yield the title product as an off-white solid (2.99 g).

^{1}H NMR (DMSO) : δ 2.84-2.88 (4H, bs), 3.34 (4H, bs), 5.11 (2H, bs), 6.54-6.58 (1H, m), 6.69-6.71 (1H, m), 6.82-6.92 (2H, m)

MS : $C_{12}H_{14}F_3N_3O$ requires 273; Found 274 (MH^+)

Description 6

3-{2-[4-Trifluoroacetyl-piperazin-1-yl]-phenylamino}-but-2-enoic acid ethyl ester (D6)

2-(4-trifluoroacetyl-piperazin-1-yl) aniline (D5) (0.77 g, 2.7 mmol), ethylacetoacetate (0.36 g, 2.7 mmol) and acetic acid (0.17 ml) were stirred in toluene (5mL) and then refluxed in Dean-Stark apparatus. The solvent was evaporated *in vacuo* and the residue purified by flash chromatography (EtOAc/hexane) to yield the title product as a clear oil (0.12 g)

^{1}H NMR ($CDCl_3$) : δ 1.25-1.30 (3H, t), 2.12 (3H, s), 2.94-2.97 (4H, m), 3.80-3.82 (2H, m), 3.89-3.91 (2H, m), 4.13-4.18 (2H, q), 4.73 (1H, s), 6.99-7.14 (4H, m), 10.70 (1H, s)

MS : $C_{18}H_{22}F_3N_3O_3$ requires 385; Found 386 (MH^+)

Description 7

1,4-Dihydro-2-methyl-8-(4-trifluoroacetylpiperazin-1-yl)-1*H*-quinoline-4-one (D7)

(3-{2-[4-(Trifluoroacetyl)-piperazin-1-yl]-phenylamino}-but-2-enoic acid ethyl ester (D6) (117 mg, 0.30 mmol) was refluxed in diphenyl ether (1 ml) for 30 min. The solution was then eluted through a Sep-Pak column (EtOAc/hexane, then MeOH) to give the title product as a brown oil (84 mg).

^{1}H NMR ($CDCl_3$) : δ 2.44 (3H, s), 3.08 (4H, bs), 3.20 (1H, bs), 3.65 (1H, bs), 4.13 (1H, bs), 4.63 (1H, bs), 6.13-6.14 (1H, d), 7.24-7.31 (1H, m), 7.40-7.43 (1H, dd), 8.13-8.16 (1H, dd), 9.08 (1H, bs)
MS : $C_{16}H_{16}F_3N_3O_2$ requires 339; Found 340 (MH^+)

Description 8

4-Chloro-2-methyl-8-(4-trifluoroacetyl-piperazin-1-yl)-quinoline (D8)

1,4-Dihydro-2-methyl-8-(4-trifluoroacetylpiperazin-1-yl)-1*H*-quinoline-4-one (D7) (84 mg, 0.25 mmol) was refluxed in $POCl_3$ (2 ml) for 2 h. The solution was then diluted with water (5 ml) and basified with 2*M* NH_4OH. Reaction mixture was then extracted with DCM (2 x 10ml) and the combined organic layers washed with water (20 ml), dried ($MgSO_4$), and the solvent evaporated *in vacuo* to give the title product as a brown oil (88 mg).
^{1}H NMR ($CDCl_3$) : δ 2.73 (3H, s), 3.42-3.49 (4H, m), 3.93-3.97 (2H, m), 4.01-4.05 (2H, m), 7.13-7.16 (1H, d), 7.41 (1H, s), 7.45-7.52 (1H, t), 7.87-7.91 (1H, dd)
MS : $C_{16}H_{15}ClF_3N_3O$ requires 357; Found 358 (MH^+)

Description 9

2-Methyl-4-phenylsulfonyl-8-(4-trifluoroacetyl-piperazin-1-yl) quinoline (D9)

4-Chloro-2-methyl-8-(4-trifluoroacetyl-piperazin-1-yl)-quinoline (D8) (88 mg, 0.25 mmol) was dissolved in DMF (5 ml) under argon. Phenylsufinate sodium salt in DMF (5 ml) was added and the solution heated to 100 °C for 16h. Reaction mixture was then diluted with water (10 ml) and extracted with EtOAc (2 x 10 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$) and the solvents evaporated *in vacuo* to give the title product as a brown oil (mg).
^{1}H NMR ($CDCl_3$) : δ 2.86 (3H, s), 3.39-3.43 (4H, m), 3.91-3.93 (2H, m), 3.99-4.01 (2H, m), 7.11-7.13 (1H, d), 7.44-7.59 (4H, m), 7.95-7.96 (2H, d), 8.14 (1H, s), 8.20-8.22 (1H, dd)
MS : $C_{22}H_{20}F_3N_3O_3S$ requires 463; Found 464 (MH^+)

Example 1

4-Phenylsulfonyl-8-piperazin-1-yl quinoline (E1)

8-(4-*tert*-Butyloxycarbonyl-piperazin-1-yl)-4-phenylsulphonyl quinoline (D2) (51.2 mg, 0.11 mmol) was stirred with 20 % trifluoroacetic acid in DCM (10ml) for 1h. Solvents were then evaporated *in vacuo* and the residue partitioned between DCM (10ml) and sat. $NaHCO_3$ (10 ml). Aqueous layer re-extracted and the combined organic layers washed with brine (10 ml), dried ($MgSO_4$) and the solvents evaporated *in vacuo*. Purification by sep-pak chromatography (MeOH / NH_3 / DCM) gave the title product as a yellow solid (25.7 mg).
^{1}H NMR ($CDCl_3$) : δ 3.25-3.27 (4H, m), 3.38-3.40 (4H, m), 7.18-7.19 (1H, dd), 7.50-7.59 (4H, m), 7.97-7.99 (2H, dd), 8.18-8.19 (1H,d), 8.21-8.24 (1H, dd), 9.07-9.08 (1H, s)
MS : $C_{19}H_{27}N_3SO_4$ requires 353; found 354 (MH^+)

Example 2

4-Phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E2)

4-Phenylsulfonyl-8-piperazin-1-yl-quinoline (E1) (25.7 mg, 0.75 mmol) was dissolved in DCM (5ml) and 1*M* HCl in ether (80 µL, 0.80 mmol) was added. Solvent evaporated *in vacuo* to give the title product as an orange solid (26.9 mg).

^{1}H NMR : δ 3.73 (8H, bs), 7.55-7.75 (5H, m), 8.00-8.02 (2H, d), 8.38-8.39 (1H, d), 8.50-8.52 (1H, d), 9.35-9.35 (1H, d), 10.15 (2H, bs)

Example 3

2-Methyl -4-phenylsulfonyl-8-piperazin-1-yl-quinoline (E3)

2-Methyl-4-phenylsulfonyl-8-(4-trifluoroacetyl-piperazin-1-yl) quinoline (D9) (106 mg, 0.23 mmol) was dissolved in MeOH (5 ml) and water (1.5 ml). K_2CO_3 was added and the solution stirred for 90 min. The solvent was evaporated *in vacuo* and the residue partitioned between DCM / MeOH (10 ml) and water (10 ml). The aqueous layer was re-extracted with DCM / MeOH (10 ml) and the combined organics washed with brine (20 ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give the title product as an orange oil (88 mg).

^{1}H NMR ($CDCl_3$) : δ 2.86 (3H, s), 3.17-3.20 (4H, m), 3.30-3.34 (4H, m), 7.11-7.14 (1H, dd), 7.40-7.57 (4H, m), 7.94-7.97 (2H, m), 8.10-8.13 (2H, m)

~~MS : $C_{20}H_{21}N_3O_2S$ requires 367; Found 368 (MH^+)~~

Example 4

2-Methyl-4-phenylsulfonyl-8-piperazin-1-ylquinoline hydrochloride (E4)

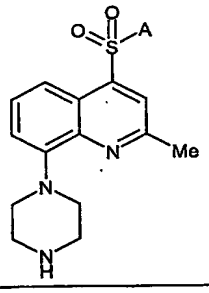
2-Methyl -4-phenylsulfonyl-8-piperazin-1-yl-quinoline (E3) (88 mg, 0.23 mmol) was taken up in DCM and 1*M* HCl in ether (0.274 ml) added. Solvents evaporated *in vacuo* to give the title product as a brown solid (93 mg).

^{1}H NMR ($CDCl_3$) : δ 3.06 (3H, s), 3.92 (8H, bs), 7.56-7.59 (2H, m), 7.64-7.7[illegible] H, m), 8.00-8.01 (2H, d), 8.24 (1H, bs), 8.28 (1H, s), 8.58-8.60 (1H, d), 10.35 (2H, bs)

MS : $C_{20}H_{21}N_3O_2S$ requires 367; Found 368 (MH^+)

Examples 5-7

Examples 5-7 were prepared in an analogous manner to Example 3



Example	A	MH^+	Formula
5	2-fluorophenyl	386	$C_{20}H_{20}FN_3O_2S$
6	3-fluorophenyl	386	$C_{20}H_{20}FN_3O_2S$
7	3-chlorophenyl	402	$C_{20}H_{20}ClN_3O_2S$

Pharmacological data

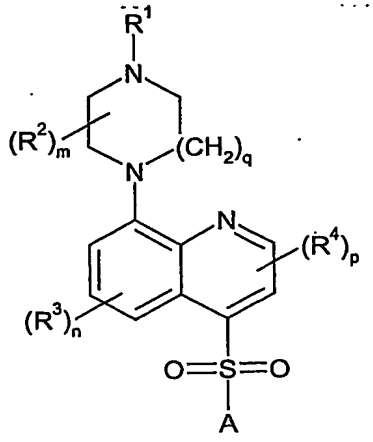
Compounds can be tested following the procedures outlined in WO98/27081.

The compounds of Examples E1- E7 were tested and showed good affinity for the 5-HT_6 receptor, having pKi values > 8 at human cloned 5-HT_6 receptors.

5

Claims:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 independently represent hydrogen or C_{1-6} alkyl or R^1 is linked to R^2 to form a group $(CH_2)_2$, $(CH_2)_3$ or $(CH_2)_4$;

m represents an integer from 1 to 4, where m is greater than 1, two R^2 groups may instead be linked to form a group $(CH_2)_2$, $(CH_2)_3$ or $(CH_2)_4$;

R^3 and R^4 independently represent hydrogen, halogen, cyano, $-CF_3$, $-CF_3O$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR^5R^6$;

R^5 and R^6 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

n represents an integer from 1 to 3;

p and q independently represent 1 or 2.

A represents a group $-Ar^1$ or a group $-Ar^2$-Ar^3;

Ar^1, Ar^2 and Ar^3 independently represent an aryl group or a heteroaryl group, both of which may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $CONR^7R^8$ or $SO_2NR^7R^8$, wherein R^7 and R^8 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom; or solvates thereof.

2. A compound according to claim 1 which is a compound of formula E1-E7 or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2 for use in therapy.

4. A compound according to claim 1 or claim 2 for use in the treatment of depression, obesity, anxiety and cognitive memory disorders.

5. A pharmaceutical composition which comprises a compound according to claim 1 or claim 2 and a pharmaceutically acceptable carrier or excipient.

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